REVIEW

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Are GnRH and FSH potentially damaging factors in the cardiovascular system?

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In the physiological view the human cardiomyocytes express receptors of gonadotropin-releasing hormone and follicle-stimulating hormone. The local effects of these hormones in the heart are related also to some interstitial cells, such as endothelial cells with follicle-stimulating hormone receptors and immune cells with gonadotropin-releasing hormone receptors. The administration of androgen deprivation therapy in patients with prostate cancer is associated with increased incidence of cardiovascular complications. It is suggested that negative action of this therapy on cardiovascular system is due to the loss of testosterone but also levels of gonadotropin-releasing hormone and follicle-stimulating hormone are changed by therapy. In this article we review the literature to date with an emphasis on recent investigation focused on potential role of abnormal gonadotropin-releasing hormone and follicle-stimulating hormone levels induced by gonadotropin-releasing hormone agonists on the cardiovascular risk. These facts exacerbate the complexity of specific hormone and cell relationships within heart and vessels. Androgen deprivation therapy reveals the physiological relationships between hormones and specific tissues that are not part of the endocrine system.

1. Introduction

In clinical practice, androgen deprivation therapy (ADT) is frequently used for treatment of prostate cancer. While ADT reduces the risk of prostate cancer-specific mortality, it is associated with adverse effects on cardiovascular (CV) system in treated men. In patients with ADT, several studies support the evidence for acute myocardial infarction (MI), arrhythmias, stroke, heart failure, and thrombosis (Haque et al. 2017; Scailteux et al. 2016; Sun et al. 2016; Poljak et al. 2016; O'Farrell et al. 2015; Bosco et al. 2015; Carneiro et al. 2015).

Although the higher prevalence of cardiac disease may be related to preexisting CV morbidity in these patients, ADT with GnRH agonists likely has direct and indirect CV effects. Additional research is necessary to define relevance of GnRH and FSH and their receptors in heart and vessels. Better understanding of cardiotoxicity of ADT is important, because of CV disease, rather than prostate cancer itself, is the most common cause of mortality in men with early stage prostate cancer (Conteduca et al. 2013).

In 2010, the American Heart Association issued a statement confirming the possible association between ADT and adverse CV events (Levine et al. 2010). The European Association of Urology specified in its 2013 prostate cancer guidelines the need for special attention to the risk-to-benefit ratio of ADT in patients with a higher risk of CV events (Heidenreich et al. 2014).

Cardiac damage induced by ADT could have a dual origin. Indirectly, ADT CV risk is associated with an increase in body weight, insulin resistance, dyslipidemia. Direct effects are thought to occur *via* cardiomyocytes that express the receptors for androgen, GnRH and FSH (Tivesten et al. 2015; Kakar and Jennes 1995). The presence of GnRH receptors was confirmed also on T lymphocytes and macrophages (Bosco et al. 2015; Tanriverdi et al. 2005). The FSH receptor is expressed on endothelial cells. At present there is still a relative paucity of data regarding the influence of ADT on signalling pathways in cardiac and endothelial cells. From a physiological view the better description of the signal effect of FSH and GnRH in heart and vessels is needed. In this review we present the role of abnormal GnRH and FSH levels induced by ADT on the CV risk. Improved understanding of the mechanisms involved in the effects of ADT on the CV health may reveal mechanisms involved in the increase of susceptibility to CV diseases and interaction between heart and the hypothalamic–pituitary–testes axis.

2. Type of ADT and cardiovascular risk

Different forms of ADT have various effects on hormonal levels (summarized in the Table 1) (Greiman and Keane 2017, Scailteux et al. 2016). The meta-analysis of Carneiro et al. (2015) showed that ADT is associated with significant adverse effects from 13 trials (n = patients) and authors concluded that ADT in patients with prostate cancer (therapy for at least 6 months) increased CV morbidity for acute MI as well as increased the incidence of non-fatal events such as arrhythmias, stroke, non fatal MI, heart failure, and thrombosis (Carneiro et al. 2015). A meta-analysis of population-based studies showed that antiandrogens had no effect

Table 1. Androgen deprivation therapy and their relationship to hormonal changes.

ADT	Hormone		
	Testosterone	GnRH	FSH
Orchiectomy	↓	↑	↑
GnRH agonist	↑ ↓	**potentially hyperactive GnRH downstream effects**	↑↓↑
GnRH antagonist	↓	**blocked GnRH receptors and downstream effects**	↓

The first arrow indicates initial effects while the second and the third arrow indicate secondary and tertiary effect (modified according to Shore et al., 2013).
Abbreviations: androgen deprivation therapy (ADT), follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH)

on the CV risk. Higher risks of CV disease were seen in patients with orchidectomy compared to GnRH agonist treated patients. Another data found a similar risk of CV disease between medical and surgical treatment as androgen deprivation therapy for prostate cancer (Thomsen et al. 2017).

GnRH antagonists competitively and reversibly bind to GnRH receptors and lead to rapid suppression of testosterone release without an initial testosterone flare (Klotz et al. 2008) and were associated with a significantly lower risk of CV events within the first year of the starting therapy (HR 0.44, 95% CI 0.26–0.74) (Albertsen et al. 2014). Antagonists are also associated with a reduced risk of CV events in men with pre-existing CVD, compared with agonists (Greiman and Keane 2017). But according to some authors the difference between GnRH antagonists to agonists appears to be rather low (Scailteux et al. 2017). The hypothesis that GnRH antagonists lower cardiovascular complications when compared with agonists requires additional testing (Albertsen 2017). Cardiotoxicity of GnRH agonists and antagonists is an area of intense ongoing investigation.

ADT with GnRH agonists has been a mainstay of therapy for locally advanced and metastatic prostate cancer since the 1990s and is also increasingly used in the neoadjuvant setting prior to radiotherapy for early stage prostate cancer. Bosco et al. (2015) showed associations between GnRH agonists and nonfatal or fatal MI RR: 1.57 (95% CI, 1.26–1.94) or stroke RR: 1.51 (95% CI, 1.24–1.84). Meta-analysis of eleven observational studies showed that antiandrogen was associated with a 30% decrease risk for MI compared to GnRH agonists (RR, 0.70 [0.54–0.91]) (Scailteux et al. 2016). A comparative effectiveness study suggested that the risk of CV disease was higher for men treated with GnRH agonist therapy than for those treated with orchiectomy (Sun et al. 2016). In general, the outcomes from studies about an association of GnRH agonist therapy with increased risk of CV diseases are problematic due to missing data (type of ADT, CV disease severity, risk factors). The study by O'Farrell et al. (2015) was unique because researchers had access to a drug register and defined ADT type and duration and the patients´ history of CV disease. These authors analyzed CV risk among 41 362 men with ADT in prostate cancer patients and 187 785 men without prostate cancer. The study showed an increased risk of developing CV diseases in men with prostate cancer treated with GnRH agonists (O'Farrell et al. 2015). Recent data provide optimism for a better understanding of molecular and cellular pathomechanisms of increased CV risk in patients treated with GnRH agonists.

3. Direct effects of GnRH agonists on the cardiovascular system

The effects of GnRH agonists have been analyzed in several studies since 1976. GnRH agonists bind to GnRH receptors. Sustained pituitary overstimulation by GnRH agonists causes a downregulation of GnRH receptors and an uncoupling of the GnRH signal transduction mechanism. A decrease in LH and FSH, together with the downregulation of gonadal receptors for LH and FSH, causes a complete reduction of testosterone levels.

The agonistic and antagonistic GnRH analogs were shown to exert a direct effect on the target cells in many organs through GnRH receptor coupling (Crawford et al. 2017). Thus, it can be assumed that long-term treatment with a GnRH agonist can affect cardiomyocytes by GnRH receptor signalling pathways. Moreover, GnRH agonists are degraded and eliminated from plasma more slowly than the natural GnRH. It was shown that in the coronary artery disease the GnRH signalization is hyperactive.

Another potential explanation for CV toxicity of GnRH agonists may be related to the GnRH receptor, which is expressed on T lymphocytes (Chen et al. 1999) and macrophages in atherosclerotic plaques (Min et al. 2009). This could explain the increase of cerebrovascular and coronary artery diseases observed with GnRH agonists.

Thus, from the present knowledge, we can summarize the CV effects of GnRH analogs, especially on cardiomyocytes and immune cells within atherosclerotic plaques.

3.1. The effects of GnRH in cardiomyocytes

A direct GnRH agonist effect on heart could be mediated *via* GnRH receptors that have been found in the cardiomyocytes (Kakar and Jennes 1995). Dong et al. (2011) found that GnRH is capable of regulating cardiac contractile function *via* a GnRH receptor/protein kinase A (PKA)-dependent mechanism. GnRH activates PKA, which has multiple targets for the phosphorylation in cardiomyocytes, including phospholamban, the L-type Ca_{2+} channel on the sarcolemma and components of the contractile apparatus. This effect is specific to the intact GnRH signal molecule.

GnRH agonists may directly influence heart rhythm through GnRH cardiac receptors in mice (Dong et al. 2011). In rats, GnRH was reported to the increase heart rate and blood pressure, whereas GnRH antagonists trigger hypotension and bradycardia. In clinical studies prolonged QT intervals were recorded in agonist treated prostate cancer patients (Garnick et al. 2004). However, the hemodynamic and cardiac effects of GnRH in humans remain to be established. A plethora of evidence suggests that treatment with GnRH agonists could lead to dysfunction of the cardiac receptors regulating cardiac contractility and intracellular calcium ions.

3.2. GnRH agonists and vessel remodelling through receptors on immune cells

Preclinical data by Hopmans et al. (2014) and Knuttson et al. (2016) showed the increased cerebrovascular and coronary heart diseases induced by GnRH agonists and demonstrated that GnRH agonists increase plaque vulnerability. Specifically, the study of Hopmans et al. (2014) investigated the effects of different ADT modalities on the development of atherosclerosis in a mouse model. Orchiectomy and GnRH agonist treatment more than doubled the amount of atherosclerotic plaque lesion compared with control. On the contrary, the aortic atherosclerotic plaque in mice treated with a GnRH antagonist was not significantly different from that of control animals. Moreover, the necrotic core area of the plaques in GnRH antagonist-treated mice was significantly smaller than that of GnRH agonist-treated and orchiectomized mice (Hopmans et al. 2014). Plaque necrosis is considered to increase the risk of plaque rupture, the major cause for development of acute CV events, such as MI and stroke. Another preclinical study showed that the GnRH receptor agonist leuprolide was associated with induction of necrosis in certain types of atherosclerotic plaques, while no such effect was observed in mice treated with the GnRH receptor antagonist degarelix (Knuttson et al. 2016).

GnRH receptors are expressed in both stable and more advanced atherosclerotic plaques on T-lymphocytes and macrophages of lesions. Their activation stimulate the proliferation and activity of T cells and macrophages (Tanriverdi et al. 2005). The risk of plaque rupture is increased by IFN-γ. Activation of GnRH receptors on T-lymphocytes stimulates T-cell proliferation and differentiation towards Th1 phenotype producting IFN-γ. Proinflammatory cytokines such as IFN-γ reduce collagen synthesis, increase collagenase expression and apoptosis of smooth muscle cells. Thus GnRH agonists induce a proinflammatory environment within the plaque by stimulating Th1 cells to release RANKL, IFN-γ, and TNF-α. RANK can be activated by RANKL released by Th1 cells, stimulating their differentiation to osteoclasts. Within the plaque, osteoclasts can resorb calcified regions and further contributing to plaque instability. Thus, it is assume that the stimulation of GnRH receptors on T-lymphocytes by GnRH agonists may increase destabilization of atherosclerotic plaques, rupture risk and subsequent thrombotic complications.

GnRH receptor expression was detected on some plaque macrophages. It is known that GnRH participates in macrophage function (Min et al. 2009) and macrophages play an important role in atherosclerotic plaque destabilization through the release of extracellular tissue degrading matrix metalloproteinases (MMPs). However, a recent study did not observe an increased expression of MMP-9 or decreased collagen levels in the stable distal lesions. Therefore, authors suppose that their observations argue against a role for macrophage GnRH receptor activation in GnRH agonist-induced atherosclerotic plaque necrosis (Knuttson et al. 2016).

4. Association of FSH with the cardiovascular system in context with ADT

GnRH agonists induce an initial increase in FSH levels followed by a gradual decrease to approximately 50% of normal levels, but later FSH rises gradually (Klotz et al. 2008; Lepor et al. 2012). The early CV outcome and changes in FSH levels were reported in a randomized controlled study (Margel et al. 2017). This study suggests that CV events may develop early in patients receiving a GnRH agonist compared to an antagonist and these events may be linked to the reduced suppression of FSH during the therapy. In patients, FSH decreased from pre-ADT levels by a median of 93% among antagonist arm compared to 27% reduction in the agonist arm (Margel et al. 2017). Within the agonist arm, patients with a lower than 30% FSH decrease had a 50% probability of a CV event, compared to only 12.5% of patients with a higher effect on FSH levels. These results indicate a really complex interaction between hormonal levels and further studies are needed to understand the interactions and CV effects of FSH during ADT. From a physiological point of view the information about the CV role of FSH is rare. Until now, there are only a few studies on molecular and physiological consequences of FSH system activation in the CV system.

FSH could have a potential role in CV endocrinology by two mechanisms: the direct way is related to the presence of FSH receptors on the cardiomyocytes and the endothelium, indirectly it acts through increased body weight, insulin resistance and lipid profile changes.

4.1. The direct FSH role in cardiovascular risk

FSH is a trophic hormone that is involved in metabolism, angiogenesis, protein synthesis, cell division, growth and differentiation. Within the CV system, the FSH receptors are located on the endothelium and FSH promotes angiogenesis through a VEGF-dependent mechanism (Albertsen et al. 2014; Stiley et al. 2014). Changes in the wall structure and vascular remodeling could be associated with endothelial FSH/FSH receptor signalling, thus FSH could have an important role in the vascular biology. FSH receptors are highly expressed in cardiac myocytes (Pinthus 2015; Tivesten et al. 2015). Changed levels of FSH during GnRH agonist treatment could affect the action of cardiomyocytes but this hypothesis is currently underway.

4.2. The indirect effect of FSH on cardiovascular risk

Experimental and clinical data indicate that FSH may contribute to CV effects associated with ADT through its role in inflammation, atherosclerosis, insulin resistance, formation of reactive oxygen species, and adipocyte rearrangement (Crawford et al. 2017). Studies in mice showed that dysfunctional fat *in vivo* accumulates in a FSHR concentration–dependent manner (Liu et al. 2015). Dysfunctional fat plays a key pathogenic role in the development of metabolic syndrome and CV diseases (Hajer et al. 2008). Adipokines, secreted by adipocytes are associated with the development of the insulin resistance and atherosclerotic disease (Choi et al. 2013).

Vascular inflammation, involved in the early and late events of endothelial dysfunction, contribute to atherosclerosis risk. Endothelial dysfunction is a significant predictor of CV events. In the study Figueroa-Vega et al. (2015) FSH levels correlated with vascular inflammation. Thus, during GnRH treatment the increased FSH level could contribute to atherosclerotic risk. It is known that calcified plaques are at least 4- to 5-times stiffer than cellular atherosclerotic plaques. FSH signalling is also involved in reabsorption of calcified regions within plaques thus FSH increase the likelihood of the rupture and CV event (Crawford et al. 2017).

5. Conclusion

The administration of ADT in patients with prostate cancer is associated with increased incidence of fatal and non-fatal cardiovascular complications, such as MI, heart failure, stroke and others. Clinicians should carefully consider a range of cardiovascular risk factors before prescribing ADT to patients based on the patient's cardiac history. The presence of GnRH and FSH receptors was confirmed on cardiomyocytes. The endothelial cells express FSH receptors and within atherosclerotic plaque the T lymphocytes and macrophages express GnRH receptors. However, we still do not know the clearly signal effects of GnRH and FSH in the heart and vessels. ADT could change expression and presence of GnRH and FSH receptors in the cardiovascular structures. It is also possible that future therapeutic strategies in CV diseases will affect the signalling pathways of GnRH and FSH in heart and vessels. Thus, it is necessary to understand the direct mechanisms of the various ADT modalities on cardiomyocytes, cardiac interstitium and vessels with attention how changes of FSH and GnRH affect the cardiovascular health.

Cardiotoxicity of ADT is an area of intense ongoing investigation. Recent data provide the potential for a better understanding of molecular and cellular pathomechanisms of increased CV risk in patients treated with GnRH agonists. The assimilation of these results into a meaningful approach to these patients relies on the continued multidisciplinary partnership.

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